Prostatic Diseases and Male Voiding Dysfunction

Fatty Acid Amide Hydrolase Inhibitor Treatment in Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome: An Adaptive Double-blind, Randomized Controlled Trial

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OBJECTIVE To examine the effect of a peripherally active fatty acid amide hydrolase (FAAH) inhibitor ASP3652 on safety and efficacy outcomes in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Inhibition of FAAH is hypothesized to reduce the excitability of urinary tract afferents including nociceptors.

MATERIALS AND METHODS In this adaptive, randomized, double-blind, placebo-controlled study, adult male patients with moderate to severe CP/CPPS were treated for 12 weeks with an oral dose of ASP3652 (25, 75, 150, or 300 mg twice daily, or 300 mg once daily), or placebo. A Bayesian model was used for adaptive prospective modeling of randomization, study continuation decisions, and analysis of the efficacy variables.

RESULTS The study was stopped for futility at preplanned interim analysis when 239 patients were randomized (226 were included in the intention-to-treat set): the 25 mg group showed the largest reduction of the primary end point National Institutes of Health Chronic Prostatitis Symptom Index total score (7.0 points), but the placebo group showed a mean reduction of 7.3 points (difference: 0.3 [95% confidence interval: −1.9, 2.6]). Micturition outcomes improved compared with placebo in all ASP3652 groups; for example, in the 300 mg twice daily group, voiding frequency decreased by −1.10 (95% CI: −2.0, −0.2) voids/24 hours vs placebo. Safety outcomes were comparable across the treatment groups.

CONCLUSION ASP3652 was generally safe and well-tolerated. It did not show efficacy on pain symptoms in patients with CP/CPPS. However, the results indicate that FAAH inhibition may attenuate lower urinary tract symptoms. Dedicated studies in patients with lower urinary tract dysfunction are needed to confirm this. UROLOGY ■■: ■■–■■, 2017. © 2017 Elsevier Inc.

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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common urologic diagnosis in men and is associated with significant pain, urinary symptoms, and reduction in quality of life (QoL).[1] Successful management of this condition is challenging and often inadequate, indicating a need to develop novel and effective therapies.[1,2]

Fatty acid amide hydrolase (FAAH) is a synaptic membrane enzyme responsible for the breakdown of endogenous cannabinoids (eCBs). Naturally occurring eCBs and exogenous cannabinoids such as delta-9-tetrahydrocannabinol directly stimulate cannabinoid receptors, including receptor subtypes CB1 and CB2.[3,4] Activation of the CB1 receptor reduces activity and excitability of nociceptors.[5,6]

By inhibiting FAAH, the levels of eCBs at activated sites (eg, local afferent nerves) are hypothesized to increase, thereby reducing pain in CP/CPPS. Treatment with centrally acting CB agonists can induce cannabinoid-like side effects, such as psychoactive and motor effects.[7] Peripheral FAAH inhibition may not induce these central effects. ASP3652 is an orally available small molecule FAAH inhibitor with minimal central nervous system penetration. Internal Astellas data from animal models showed ASP3652 to be active on pain, voiding frequency, and bladder volume. ASP3652 appeared to increase eCBs in a dose-dependent way in plasma and to have a good safety profile in various healthy human volunteer studies in which more than 350 subjects were exposed to ASP3652 (Internal Astellas data).

MATERIALS AND METHODS

This was an adaptive, randomized, double-blind, placebo-controlled, parallel group, multidose level clinical trial with a treatment period of 12 weeks (ClinicalTrials.gov Identifier: NCT01391338). Adult male patients with CP/CPPS[8] of moderate to severe intensity were enrolled. Key selection criteria are presented in Supplementary Table S1. The protocol and amendments were reviewed by an independent ethics committee for each study site. Approval for the study protocol was obtained from the relevant competent authorities prior to study initiation. The study was conducted in accordance with the ethical principles that have their origin in the 1964 Declaration of Helsinki and its later amendments, Good Clinical Practice, International Conference on Harmonisation, guidelines, and applicable laws and regulations. An independent ethics committee-approved written informed consent was obtained from all individual participants included in the study prior to the initiation of any study-specific procedures.

During the treatment period, the patients received ASP3652 (25, 75, 150, or 300 mg twice daily, or 300 mg once daily) or matching placebo. The dose range for the study was selected based on modeling and simulation of nonclinical and phase 1 clinical pharmacokinetic and pharmacodynamic data. The study was conducted between June 2011 and February 2013 at 35 centers in 6 European countries (Czech Republic, Germany, Latvia, Lithuania, Poland, and Spain).

The primary end point was change in total score from baseline to week 12 in the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI).[9,10] This score combines aspects of 3 important symptom domains of CP/CPPS (pain, micturition, and QoL), with higher scores indicating higher disease severity. A key secondary outcome was mean daily pain: the mean of average daily pain severity scores (on a 0-10 numerical rating scale), measured on 7 consecutive days before study visits. Other secondary efficacy parameters included International Prostate Symptom Score (IPSS) and micturition diary parameters. During the week prior to study visits, the patients were asked to complete a 3-day voiding diary recording micturition episodes and perceived level of urinary urgency by means of the Patient Perception of Intensity of Urgency Scale.[11]

Clinical responders were defined as subjects who indicated marked or moderate improvement on a 7-grade global response assessment (GRA responders) and subjects who had a decrease of 6 or more points in the primary end point (NIH-CPSI responders).

To identify the effects of ASP3652 on mood and drug withdrawal, specific questionnaires were incorporated, that is, the Profile of Mood States questionnaire[12] and Physician Withdrawal Checklist.[13]

Statistical Design and Analyses

In clinical research, adaptive trial design has been proposed as a means to increase the efficiency of randomized clinical trials.[14] In the current study, a Bayesian (ie, prospective updating the probability for a hypothesis as more evidence or information becomes available) adaptive trial design was employed to facilitate dose selection by allocating most patients to the maximum effective study group; it also enabled early stopping of the study if and when outcomes were either very beneficial ("success") or absent ("futility"). The Bayesian design used accumulating efficacy and safety data for preplanned interim analyses to adjust the probability of randomizing patients to individual treatment groups.[15] An initial "burn-in" period consisting of 60 randomized patients (10/group, randomized 1:1:1:1:1:1) was performed. Thereafter, the observed data at weeks 4, 8, and 12 were used for the interim analyses for the next cohort of patients every 4 weeks favoring the maximum effective dose, that is, the highest change from baseline in primary and key secondary (NIH-CPSI pain domain) efficacy end points. In these calculations, drug safety was included by considering withdrawals due to adverse event (AE) treatment failures for whom change from baseline in end points was set to 0 in the interim analyses. The allocation algorithm strived to achieve a similar sample size in the placebo group and maximum effective dose group. An independent data monitoring committee (DMC) performed the unblinded interim evaluations and made recommendations to stop or continue the trial.

The sample size for this study was explored through Bayesian clinical trial simulations: assuming that at least 1 dose group achieved a clinically relevant effect in the NIH-CPSI total score compared with placebo (ie, reduction of 4 points or more[10]) and a standard deviation of 7, a total of 350 subjects would be sufficient to demonstrate that the probability that the best dose is found to be superior to placebo is at least 95%.

Bayesian posterior predictive probabilities (ranging from 0 to 1) were calculated for the adaptive interim analyses as well as for the final analysis at the end of the study. The probability that a certain dose was better than placebo was used, either by the futility difference (ie, a mean difference vs placebo of ≥2 points in the NIH-CPSI total score) or by the clinical significant difference (CSD). After 50% of the patients were randomized, the study would be stopped for success if the probability by CSD was at least 90%. The study would be stopped for futility if the probability by futility difference was less than 20%.

Continuous secondary and exploratory variables were analyzed using non-Bayesian analysis of covariance models. A logistic regression model was used to analyze the proportion of NIH-CPSI and GRA responders. "Last observation carried forward" was utilized to impute missing values. Odds ratios (ORs) of each ASP3652 treatment group over placebo and the corresponding 2-sided 95% CI were derived. The study was powered using Bayesian statistics, therefore not designed to test a statistical hypothesis at any significant level; *P* values are therefore for the purpose of flagging potential trends only, not for rigorous assessment of statistical significance.

All non-Bayesian data processing, summarization, and analyses were performed using Statistical Analysis System (SAS institute Inc; Cary, NC, USA) or above in a Unix environment. Bayesian interim and final analyses were performed using program scripts in Fortran in a Linux environment.

RESULTS

Participants

In total, 226 patients had evaluable primary end point measurements (Fig. 1). Due to the adaptive randomization, the final number of subjects per study group differed. One randomized patient (300 mg once daily) did not receive any study medication. Demographic and baseline characteristics were similar for all 6 treatment groups (Table 1). The mean age of the patients was 45.4 years and the mean duration of CP/CPPS symptoms was more than 4 years. Pharmacodynamic analysis in subjects receiving ASP3652 showed a dose-dependent increase of eCB serum levels (data not shown).

Efficacy

After 239 patients were randomized, the study was stopped for futility at the recommendation of the DMC. The efficacy population (N = 226) included patients with an assessable primary end point, that is, a baseline and at least 1 post-baseline NIH-CPSI total score, or withdrew due to an AE, in which case the change from baseline in the primary end point was set to 0. The results of the Bayesian analysis allocated most subjects to the 25 mg twice daily dose (n = 52); this group showed a mean change from baseline to end of treatment of −7.0 points of the NIH-CPSI total score (Table 2). However, the mean decrease in the placebo group was −7.3 (calculated posterior difference: 0.3 [95% CI: −1.9, 2.6]). The probability that this dose was better than placebo was 1.9%, that is, lower than the predefined margin probability for stopping for futility (20%). The probability that the 25 mg dose was better than placebo by the CSD was less than 0.1%.

No dose-response relationship in primary and key secondary end point was observed. Also, no marked differences were observed between placebo and ASP3652 groups in QoL NIH-CPSI subdomain scores, mean daily pain (Table 2), as well as in the NIH-CPSI responder rates: 64% vs 50%-56%, respectively (OR ranging from 0.62 [95% CI: 0.24, 1.57] to 0.89 [95% CI: 0.33, 2.43]). For GRA, the responder rate was 38% vs 39%-50%, respectively (OR ranging from 0.87 [95% CI: 0.39, 1.96] to 1.79 [95% CI: 0.73, 4.41]). No treatment effect was shown in the preplanned subgroups.

The adjusted mean changes of outcomes relating to micturition appeared to be larger in all ASP3652 groups than in the placebo group. For these outcomes, the *P* values for the difference with placebo were smaller than .05 for some of the study groups (Table 2). Other derived micturition parameters (ie, nocturnal voids, mean level of urgency) also

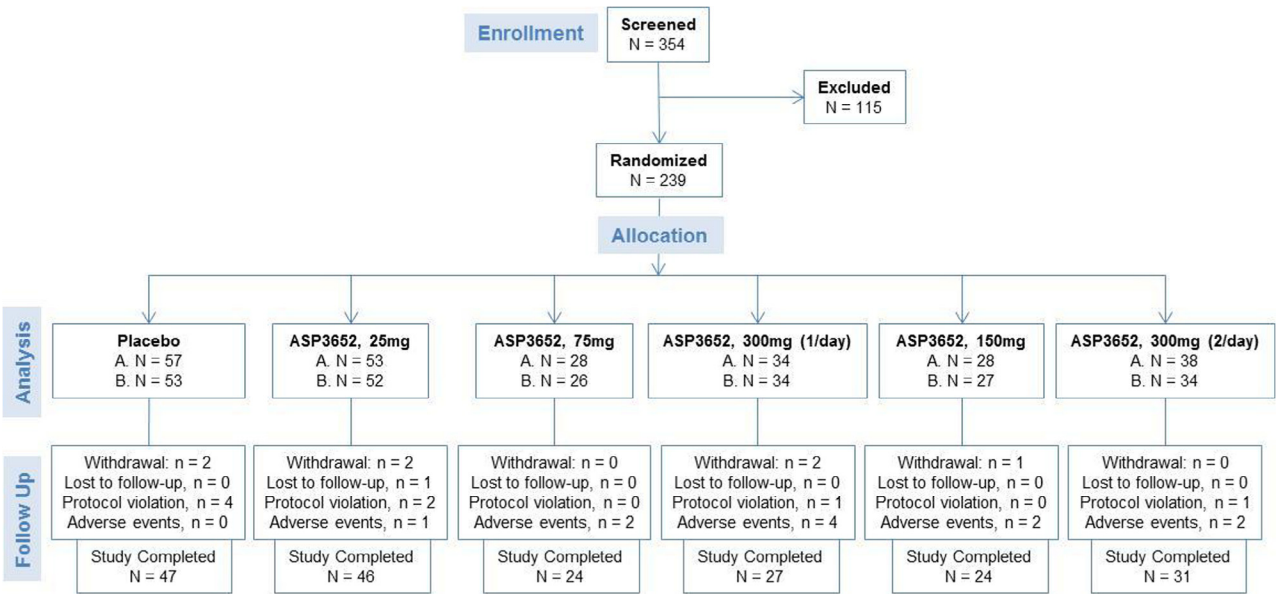

Figure 1. Flow diagram of study population (safety and efficacy population). A, safety population: all randomized patients who took at least 1 dose of double-blind study drug (N = 238; 1 patient in the 300 mg once daily dose group was randomized but was not dosed); B, efficacy population: all randomized patients who took a dose of double-blind study drug and had an National Institutes of Health Chronic Prostatitis Symptom Index total score at baseline and at least 1 post-baseline or dropped out due to an adverse event (N = 226). (Color version available online.)

Table 1. Demographics and baseline characteristics of efficacy population

Parameter	Statistic/Category	Placebo N = 53	ASP3652 25 mg (2/day) N = 52	75 mg (2/day) N = 26	300 mg (1/day) N = 34	150 mg (2/day) N = 27	300 mg (2/day) N = 34	Total N = 226
Age (years)	Mean (SD)	45.3 (12.9)	46.3 (15.5)	45.3 (11.0)	43.9 (13.3)	42.5 (14.0)	47.8 (12.6)	45.4 (13.4)
Age group	>=65 years, N (%)	3 (5.7)	7 (13.5)	2 (7.7)	3 (8.8)	3 (11.1)	4 (11.8)	22 (9.7)
Ethnicity	Caucasian, N (%)	53 (100)	52 (100)	26 (100)	34 (100)	27 (100)	34 (100)	226 (100)
BMI (kg/m)	Mean (SD)	27.6 (4.4)	26.4 (3.6)	26.8 (2.8)	25.8 (3.0)	26.3 (3.6)	27.4 (3.6)	26.8 (3.7)
Duration of symptoms (month)	Mean (SD)	60.9 (76.3)	41.9 (37.9)	60.0 (83.0)	50.5 (53.9)	37.1 (36.2)	55.1 (79.7)	51.2 (63.4)
Patients with LUTS	Frequency[a], N (%)	18 (34.0)	16 (30.8)	8 (30.8)	11 (32.4)	6 (22.2)	11 (32.4)	70 (31.0)
	Urgency[b], N (%)	7 (13.2)	3 (5.8)	1 (3.8)	2 (5.9)	3 (11.1)	3 (8.8)	19 (8.4)
	Nocturia[c], N (%)	25 (47.1)	26 (50.0)	11 (42.3)	19 (55.9)	11 (40.7)	19 (55.9)	111 (49.1)
Pain location on DRE	Pain in prostate surrounding area, N yes (%)	6 (11.3)	7 (13.5)	10 (38.5)	6 (17.6)	6 (22.2)	4 (11.8)	39 (17.3)
	Prostate-related pain, N yes (%)	25 (47.2)	32 (61.5)	12 (46.2)	19 (55.9)	14 (51.9)	19 (55.9)	121 (53.5)
	Both, N yes (%)	22 (41.5)	13 (25.0)	4 (15.4)	9 (26.5)	7 (25.9)	11 (32.4)	66 (29.2)

BMI, body mass index; DRE, digital rectal examination; LUTS, lower urinary tract symptoms.

[a] Patients with at least 8 micturitions per 24 hours at baseline.

[b] Patients with at least two nocturia episodes during one night in the baseline diary.

[c] At least one urgency episode (PPIUS grade 3 or 4) on each day in the baseline diary.

showed the same pattern (data not shown). When designing the study, it was not anticipated that the effect of ASP3652 would be more prominent on micturition than pain. As a result, no prospective subgroup analyses based on micturition end points were planned, and no adjustments for multiplicity of statistical analyses were deemed necessary. A post-hoc analysis of 70 patients with increased daily voiding frequency (see Table 1) showed that the mean reduction in voids/24 hours in the ASP3652 groups ranged from −1.87 (95% CI: −3.21, −0.53) to −3.10 (95% CI: −5.40, −0.81) vs −0.65 (95% CI: −1.89, 0.58) voids/24 hours in the placebo group.

Safety and Tolerability

Overall, 40.3% of the patients in this study experienced at least 1 AE (41.1% in the placebo group and 40.1% in the combined ASP3652 group; AEs related to study drug: 17.9% and 16.5%, respectively). There were no clinically relevant differences in specific AEs between placebo and study drug groups. The most common AEs included headache and insomnia (Supplementary Table S2). The incidence of serious AEs was low (5 in total) and similar across all groups, and none were considered to be related to the study drug. None of the patients in the placebo group discontinued treatment because of a drug related AE compared to 7 (3.8%) in the total ASP3652 group (1 in 25 mg, 75 mg, and 150 mg; 2 in 300 mg once daily and twice daily). No dose-response relationship could be observed in AEs or discontinuations.

No patients reported AEs related to mood changes, withdrawal effects, or central nervous system effects in general. The Profile of Mood States and Physician Withdrawal Checklist questionnaires did not show differences between placebo and ASP3652 (data not shown). Clinical laboratory evaluations, vital signs, and electrocardiograms did not reveal any safety concerns with ASP3652 dosing.

COMMENT

To our knowledge, this is one of the first clinical studies employing Bayesian adaptive trial design to be published for a urologic condition. The adaptive design was effectively performed and caused the study to stop early because the peripheral FAAH inhibitor ASP3652 was found to be not efficacious for CP/CPPS. By applying adaptive design techniques, the efficiency of using patient data was increased, saving 111 subjects from being treated with a drug that was unlikely to reduce their pain. A disadvantage of performing an adaptive study is the complexity of its implementation and execution,[14] involving the complex logistics of providing required data for the evaluation by the DMC and its resulting ongoing randomization updates; it therefore requires more lead time to set up than a classical study. However, this potential delay was effectively compensated by the early study termination.

Overall, 5 dose levels of up to 300 mg twice daily were safe and well-tolerated, but did not improve pain symptoms compared with placebo in men with moderate to

Table 2. Efficacy end points: values at baseline (mean [SE]), change from baseline to end of treatment (mean [SE]), and difference of change vs placebo (Δ vs placebo: mean [95% CI; *P* value])

			ASP3652				
Variable	Parameter	Placebo N = 53	25 mg BID N = 52	75 mg BID N = 26	300 mg QD N = 34	150 mg BID N = 27	300 mg BID N = 34
NIH-CPSI total score	Baseline	24.2 (0.71)	23.4 (0.73)	22.3 (0.98)	23.5 (0.78)	21.2 (0.71)	22.4 (0.90)
	EoT	17.0 (1.05)	16.1 (1.07)	14.9 (1.46)	16.6 (1.12)	13.8 (1.37)	15.6 (1.30)
	CFB*	−7.3 (0.97)	−7.0 (0.68)	−6.9 (0.69)	−6.5 (0.78)	−6.8 (0.60)	−6.7 (0.70)
	Δ vs PLC*	–	0.3 (−1.9, 2.6)	0.4 (−1.9, 2.8)	0.7 (−1.7, 3.1)	0.5 (−1.7, 2.7)	0.6 (−1.8, 2.9)
Mean daily pain	Baseline	5.1 (0.24)	4.8 (0.26)	4.5 (0.28)	4.9 (0.29)	3.9 (0.29)	4.7 (0.29)
	CFB	−1.4 (0.25)	−1.3 (0.26)	−1.0 (0.35)	−1.1 (0.34)	−1.7 (0.37)	−1.1 (0.32)
	Δ vs PLC	–	0.1 (−0.6, 0.8; 0.78)	0.3 (−0.5, 1.2; 0.44)	0.3 (−0.6, 1.1; 0.55)	−0.4 (−1.2, 0.5; 0.43)	0.2 (−0.5, 1.0; 0.54)
NIH-CPSI pain domain	Baseline	12.4 (0.38)	12.5 (0.38)	11.8 (0.54)	12.0 (0.42)	11.1 (0.45)	11.5 (0.43)
	CFB	−4.1 (0.50)	−3.8 (0.52)	−3.2 (0.73)	−3.5 (0.66)	−4.5 (0.74)	−4.1 (0.66)
	Δ vs PLC	–	0.4 (−1.0, 1.8; 0.61)	1.0 (−0.8, 2.7; 0.28)	0.6 (−1.0, 2.3; 0.45)	−0.3 (−2.1, 1.4; 0.70)	0.0 (−1.6, 1.6; 0.99)
NIH-CPSI urinary domain	Baseline	3.4 (0.33)	3.1 (0.29)	3.0 (0.41)	3.8 (0.33)	2.5 (0.35)	3.1 (0.44)
	CFB	−0.5 (0.25)	−0.7 (0.26)	−1.5 (0.36)	−1.2 (0.33)	−0.6 (0.37)	−0.8 (0.33)
	Δ vs PLC	–	−0.2 (−0.9, 0.5; 0.57)	−1.0 (−1.9, −0.1; 0.028)	−0.7 (−1.5, 0.1; 0.080)	−0.1 (−1.0, 0.8; 0.81)	−0.3 (−1.1, 0.5; 0.45)
NIH-CPSI QoL domain	Baseline	8.4 (0.30)	7.8 (0.35)	7.5 (0.39)	7.8 (0.40)	7.6 (0.34)	7.8 (0.33)
	CFB	−2.1 (0.35)	−2.6 (0.35)	−2.5 (0.50)	−1.9 (0.45)	−3.1 (0.50)	−2.5 (0.45)
	Δ vs PLC	–	−0.5 (−1.5, 0.4; 0.28)	−0.4 (−1.6, 0.8; 0.51)	0.2 (−0.9, 1.3; 0.72)	−1.0 (−2.2, 0.2; 0.10)	−0.4 (−1.5, 0.7; 0.51)
Voids per 24 hours	Baseline	7.37 (0.52)	6.90 (0.58)	6.75 (0.67)	7.17 (0.43)	6.60 (0.87)	6.67 (0.50)
	CFB	0.09 (0.30)	−0.46 (0.31)	−0.63 (0.44)	−0.60 (0.40)	−0.52 (0.44)	−1.00 (0.37)
	Δ vs PLC	–	−0.56 (−1.4, 0.3; 0.20)	−0.72 (−1.8, 0.3; 0.18)	−0.69 (−1.7, 0.3; 0.16)	−0.61 (−1.7, 0.4; 0.25)	−1.10 (−2.0, −0.2; 0.022)
Urgency episodes† per 24 hours	Baseline	1.21 (0.29)	0.61 (0.21)	0.70 (0.21)	0.91 (0.18)	1.31 (0.43)	0.92 (0.25)
	CFB	0.01 (0.17)	−0.27 (0.18)	−0.42 (0.24)	−0.30 (0.22)	−0.68 (0.24)	−0.24 (0.21)
	Δ vs PLC	–	−0.28 (−0.77, 0.20; 0.26)	−0.43 (−1.02, 0.16; 0.15)	−0.31 (−0.86, 0.23; 0.26)	−0.69 (−1.28, −0.10; 0.022)	−0.26 (−0.78, 0.27; 0.34)
IPSS total score	Baseline	7.22 (0.56)	7.54 (0.59)	8.88 (1.04)	8.82 (0.75)	6.32 (0.83)	8.39 (0.89)
	CFB	−0.01 (0.64)	−0.24 (0.66)	−2.25 (0.91)	−2.04 (0.85)	−1.01 (0.91)	−1.43 (0.82)
	Δ vs PLC	–	−0.24 (−2.05, 1.57; 0.79)	−2.25 (−4.46, −0.04; 0.046)	−2.04 (−4.14, 0.07; 0.058)	−1.00 (−3.20, 1.19; 0.37)	−1.42 (−3.47, 0.62; 0.17)

ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; EoT, end of treatment; IPSS, International Prostate Symptom Score; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PLC, placebo; QoL, quality of life; SE, standard error.

Secondary end points: the ANCOVA model for CFB is generated with 2 factors (treatment group and country) and 1 covariate (baseline score).

* NIH-CPSI total score data are outcomes of Bayesian modeling, CIs are predicted intervals, and no *P* values were calculated in the Bayesian analysis.

† Urgency episode: voiding episode with a urgency severity grade 3 or 4 on the PPIUS scale.

severe CP/CPPS. This lack of analgesic effect of FAAH inhibition was observed earlier in humans with chronic pain, contrasting data from animal models.[16] In the current study, the percentages of responders based on the NIH-CPSI total score were even higher in the placebo group compared with the ASP3652 groups. However, response based on global improvement (ie, GRA) seemed to be somewhat higher in ASP3652, with ORs of up to 1.79. The NIH-CPSI score is heavily dependent on pain,[17] whereas the global clinical response measured with the GRA may weigh symptoms other than pain, for example, lower urinary tract symptoms (LUTS).

The placebo response on NIH-CPSI total score (6.7/24.2 = 27.7%) and pain domain (4.1/12.4 = 33.1%) were in line with publications on CP/CPPS with comparable study populations and therapy duration.[18-20] The placebo response on the urinary domain was relatively smaller (14.7%) but still within the range of earlier CP/CPPS publications.[21-23] On micturition diary parameters and IPSS, however, the placebo group did not show a considerable reduction. The patient information provided before study enrollment did not focus on an expected effect on micturition. And other than in bladder pain syndrome, the pain in CP/CPPS is not necessarily perceived to be related to voiding. The patients in the current study possibly did not expect effects on micturition, which may explain the small placebo response on micturition outcomes.

Patients with significant LUTS (ie, IPSS ≥20) were excluded from the study to select a homogenous population avoiding confounding effects of voiding symptoms. Therefore, the baseline urinary parameters were mild in this study population, which is a limitation when examining drug effects on LUTS. Notwithstanding this mild urinary profile, the ASP3652 treated groups showed improvement of LUT parameters. The small placebo responses observed for urinary symptoms probably enabled the detection of these treatment effects. It has to be emphasized that the study was powered to show effects on pain and not micturition, so these effects on micturition must be interpreted with reservation. Still the observations may be considered to have some clinical relevance: the effects vs placebo on micturition frequency of ASP3652 in the total group and post-hoc LUTS group were comparable with and even higher than anticholinergic treatment in men with overactive bladder.[24]

A recent review discusses the aggregated data on the role of the endocannabinoid system in micturition and LUTS in preclinical studies, and concluded that modification of a local endogenous sensitized signal in micturition pathways would indeed be an attractive pharmacologic principle to relieve LUTS.[25] A beneficial effect on bladder capacity may underlie the urinary effects of ASP3652. In humans, a placebo-controlled study in 135 multiple sclerosis patients with overactive bladder cannabis extract showed to significantly improve urinary symptoms, including frequency and nocturia.[26] The current study was not designed to show effects on LUTS, so it would therefore be interesting to examine the effects of ASP3652 on micturition in a population with true LUT dysfunction.

CONCLUSION

The peripheral FAAH inhibitor ASP3652 was generally safe and well-tolerated. It did not show efficacy on pain symptoms in patients with moderate to severe CP/CPPS. However, the results suggest that FAAH inhibition may attenuate LUTS, which should be examined in dedicated studies.

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2017.02.029.